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Asthma as aetiology of bronchiectasis in Finland

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ABSTRACT

Background: By definition bronchiectasis (BE) means destructed structure of normal bronchus as a consequence of frequent bacterial infections and inflammation. In many senses, BE is a neglected orphan disease. A recent pan-European registry study, EMBARC, has been set up in order to better understand its pathophysiology, better phenotype patients, and to individualize their management.
Aim: To examine the aetiology and co-morbidity of BE in the capital area in Finland.
Methods: Two hundred five patients with BE diagnosis and follow up visits between 2016 and 2017 in Helsinki University Hospital were invited to participate in the study. Baseline demographics, lung functions, imaging, microbiological, and therapeutic data, together with co-morbidities were entered into EMBARC database. Clinical characteristics, aetiologic factors, co-morbidities, and risk factors for extensive BE were explored.
Results: To the study included 95 adult patients and seventy nine percent of the BE patients were women. The mean age was 69 years (SD ± 13). Asthma was a comorbid condition in 68% of the patients but in 26% it was estimated to be the cause of BE. Asthma was aetiological factor for BE if it had been diagnosed earlier than BE. As 41% BE were idiopathic, in 11% the disorder was postinfectious and others were associated to rheumatic disease, Alpha-1-antitrypsin deficiency, IgG deficiency and Kartagener syndrome. The most common co-morbidities in addition to asthma were cardiovascular disease (30%), gastroesophageal reflux disease (26%), overweight (22%), diabetes (16%), inactive neoplasia (15%), and immunodeficiency (12%). Extensive BE was found in 68% of BE patients in whom four or more lobes were affected. Risk factors for extensive BE were asthma (OR 2.7), asthma as aetiology for BE (OR 4.3), and rhinosinusitis (OR 3.1).
Conclusions: Asthma was associated to BE in 68% and it was estimated as aetiology in every fourth patient. However, retrospectively, it is difficult to exclude asthma as a background cause in patients with asthma-like symptoms and respiratory infections. We propose asthma as an aetiology factor for BE if it is diagnosed earlier than BE. Asthma and rhinosinusitis were predictive for extensive BE.

1. Introduction

Different factors may cause destruction that results in the irreversible enlargement and dysfunction of bronchi. Constant neutrophilic inflammation leads to excessive sputum production which increases the risk of recurrent airway infections. Together with chronic cough, these are the classical symptoms of bronchiectasis (BE).

BE, as an orphan lung disease, has mostly been under-researched and under-resourced. It is now recognised that BE is placing an increasing burden on healthcare systems around the world and there is an urgent need for better treatments, better clinical care, and for clinical and translational research into this condition.

In the United States, the prevalence of BE was estimated at 53 to 566 cases per 100,000 inhabitants in 2005. Prevalence increases with age and female gender [1].

The prevalence in Finland is little studied and may be underestimated. In 1992, the Finnish incidence was estimated at 2.7/100,000 [2].

In an analysis of seven European databases of BE outpatients, comprising a total of 1285 patients, 15% of the BE cases associated to chronic obstructive pulmonary disease (COPD), and 3.3% to asthma [3]. In a large Spanish study, COPD was found in 7.8% of the BE cases,

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and asthma in 5.4% [4].

In a USA registry study, where asthma and COPD were evaluated as comorbidities to BE, asthma was associated to 29% of BE patients and COPD to 20% [1]. Of these 1826 patients, 55% had radiographic findings (any dilated airways, thickened airway walls, or mucoid impaction) in more than three lobes. Any spirometric obstruction was found in 51% of the patients, 39% used inhaled corticosteroids, and 61% inhaled bronchodilators.

This study was performed in collaboration with the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC). We aimed to analyse aetiology factors for BE in Finland and risk factors for extensive (multilobar) BE.

2. Materials & methods

This study is a part of larger multicenter pan-European EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) study that was established in 2012 [5].

2.1. Patients and data collection

The present cross-sectional study focused on characterizing the population with non-cystic fibrosis BE. Patients were recruited between 08/2016–03/2018 from three different units in Helsinki University Central Hospital (HUH) catchment area: 1) Helsinki University Hospital, Heart and Lung Center; 2) Helsinki University Hospital, Skin and Allergy Hospital; and 3) Hospital of Espoo, pulmonary diseases.

Altogether 205 non-cystic fibrosis BE diagnosed patients were sent a recruitment letter and 103 patients were willing to take a part (Fig. 1). Eight patients were excluded for lack of BE diagnosis and 95 were included. The inclusion criteria were: 1) Doctor – patient relationship in HUCH; 2) Over 18 years-of-age; 3) High resolution computed tomography (HRCT) diagnosed BE; and 4) Non-cystic fibrosis BE.

The following data were collected from the hospital's database and medical records: the anamnesis of early respiratory infections and respiratory symptoms; the latest lung function; other lung diseases; smoking status; comorbidities and bacterial colonisation in the sputum or bronchoalveolar lavage samples [5,6].

Asthma was considered to be an aetiology factor if it had been diagnosed before BE and no other driver was found. Diagnosis of asthma was based on symptoms and airway reversibility shown either in spirometry (obstruction and a significant bronchodilator response by +12% in FEV1 or in FVC), or in PEF recording (+15% bronchodilator response or +20% day-to-day variability or +20% PEF level increase by asthma medication), by PEF or FEV1 decrease in exercise test (by −15%), or by moderate to severe bronchial hyperreactivity in histamine or methacholine challenge [7]. COPD was considered to be an aetiology driver to BE if it was diagnosed earlier than BE. Connective tissue diseases (CTD) were considered as an aetiology driver to BE if no other driver was found. In these cases, CTD had been diagnosed either in childhood or earlier than BE and CTD was classified severe. Patients have been reported to have post-infective aetiology of BE if hospitalized in childhood because of severe lower airway infection or suffered recurrent upper and lower airway infections but if no specific immunodeficiency or asthma or COPD had been diagnosed. Aspiration was reported as an aetiology of BE if there were typical symptoms together with pharyngeal dysfunction diagnosed by the logopedist according to the medical records. The diagnoses of other rare aethiologies, such as Kartagener syndrome and Williams-Campbell syndrome, were based on radiological findings. When no specific aetiology factor was found, was it considered to be idiopathic.

2.2. Radiographic findings

The radiologist examined high resolution computed tomography (HRCT) and computed tomography images of thorax according to the BE criteria of Naidich [8]. The number of affected lung lobes and whether the damage of the bronchus is cylindrical, varicose, or cystic were recorded. The lingula was considered to be an independent lobe. If four or more lobes were affected, the disease was considered to be extensive [1].

2.3. Statistical analyses

Two tailed z-test was used to compare proportions. Independent samples *t*-test and Mann-Whitney-U test were used to compare means and mean ranks respectively. When comparing aetiology factors for BE in different European populations, statistical significance was corrected for multiple testing and set at the level of < 0.01. Risk factors for extensive BE were analysed using logistic regression. In logistic regression

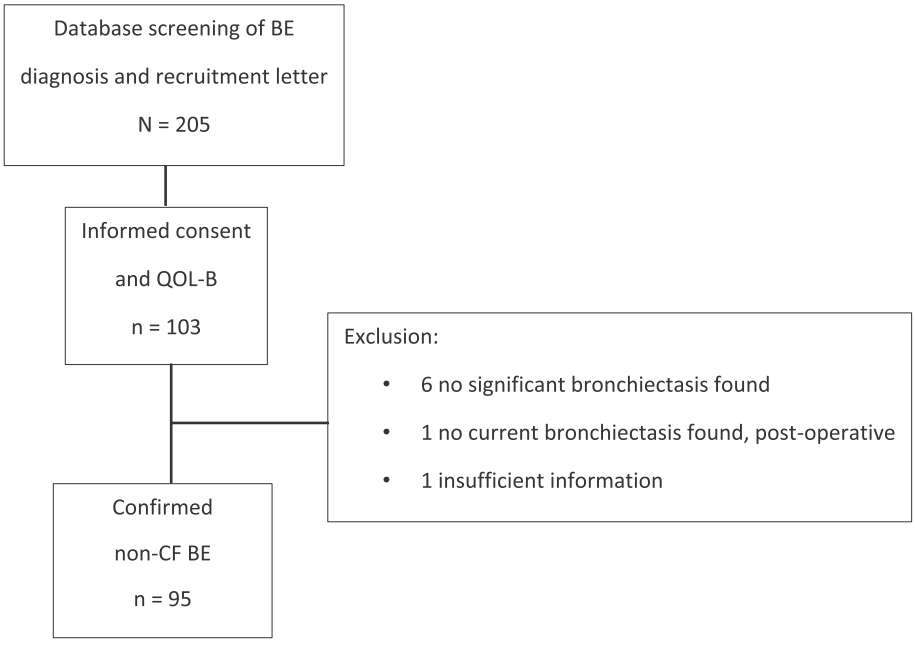

Fig. 1. Flow chart.

Table 1
Demography, comorbidities and radiology findings of the studied population.

	n = 95	
Gender, female, n (%)	75	(79)
Age, years, mean (± SD)	69	(13)
BMI, kg/m^2, mean (± SD)	26	(5)
FEV1, % predicted (± SD)	87	(24)
FVC, % predicted (± SD)	99	(21)
Current smokers, n (%)	3	(3)
Ex-smokers, n (%)	63	(66)
Chronic sputum production, n (%)	78	(82)
M. Tuberculosis, n (%)	5	(5)
P. Aeruginosa colonisation, n (%)	7	(7)
Exacerbations		
Non-hospitalized, median (± SD)	1.7	(1.6)
Hospitalized, median (± SD)	0.7	(1.4)
Comorbidities, n (%)		
Asthma	65	(68)
Cardiovascular	32	(30)
Gastroesophageal reflux disease	25	(26)
Overweight (BMI > 30)	21	(22)
Diabetes, type 2	15	(16)
Inactive neoplasia	14	(15)
Psychiatric disease (Depression/Anxiety)	13	(14)
Immunodeficiency	11	(12)
COPD	8	(8)
Aspiration	6	(6)
Rheumatoid arthritis	5	(5)
Mb.Sjögren	3	(3)
Inflammatory bowel disease	2	(2)
Primary cilia dyskinesia	1	(1)
HRCT, lobes affected, n (%)		
One lobe	3	(3.2)
Two lobes	14	(14.7)
Three lobes	13	(13.7)
Four lobes	25	(26.3)
Five lobes	17	(17.9)
Six lobes	23	(24.2)
Lobes affected, mean (± SD)	4.14	(1.47)
≥4 lobes affected	65	(68.4)
Cystic bronchiectasis, n (%)	9	(9.4)

BMI = Body Mass Index; FEV1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity; COPD = Chronic obstructive pulmonary disease; HRCT = High resolution computed tomography.

analyses, age, BMI, FEV1 (%), and FVC (%) were considered to be continuous variables. Statistical analyses were performed with the IBM SPSS Statistics program, version 22.

Ethical approval

The ethics committee of HUCH approved the study set (ethics committee registration number: 214/13/03/01/2016).

3. Results

Altogether 74% of the ninety five BE patients were women (Table 1). The mean age was 69 years (SD ± 13), 66% of the patients were ex-smokers, and 3% current smokers. Asthma was found in 69% of the patients but in only 26% it was estimated to be aetiology for BE. Asthma was considered to be aetiology for BE if asthma diagnosis had been made before BE diagnosis and if all the other aetiology factors were excluded and if the radiographic findings did not support infection for aetiology. The most common co-morbidities in addition to asthma were cardiovascular disease (30%), gastroesophageal reflux disease (26%), overweight (22%), diabetes (16%), inactive neoplasia (15%), immunodeficiency (12%), depression (10%), and anxiety (4%).

BE was considered to be idiopathic in 41% of patients, where no specific aetiology factor was found. In 11%, the disorder was post-infectious. In 5%, BE was post-tuberculosis and others were associated to rheumatic disease, Sjögren syndrome, Alpha-1-antitrypsin deficiency, IgG deficiency, and Kartagener syndrome. In 68% of patients, BE was found in four or more lobes and in 4% the BE was cystic, which is considered to be a sign of a more severe disease. In 3.2%, BE was local, affecting one lobe only, whereas in 15.8% two lobes were affected. In five patients (5%) there had been a clinical suspicion of cystic fibrosis and these patients had been tested with sweat test or genetic test, but with negative results. Two of these patients were included in the asthma group, two in the idiopathic group, and one in the immunodeficiency group.

The basal lobes of the lungs were the most often affected. In the cohort, 88% of the patients had right basal lobe changes and 85% had left basal lobe changes. The apical lobes were better preserved. Changes in the left apical lobe occurred in 31% of the patients, whereas changes in the right apical lobe occurred in 54%. The bronchial changes were mostly cylindrical and nine (9.4%) patients had cystic changes.

Comparing our findings to previous reports from Europe showed that asthma was a defined aetiology of BE in Finnish (26%), Greek (2.5%), EU (3.3%), French (4.0%), and Spanish (5.4%) studies, whereas none was found in British, Belgian, and Portuguese studies (Table 2) [3,4,9–13].

Asthma as an aetiology did not differ statistically from other aethiology factors with respect to age, BMI (body mass index), gender, smoking status, exacerbation frequency, or lung function (Table 3).

Asthma either as a comorbidity or an aethiology (OR 2.65), asthma as aethiology for BE (OR 4.25), and rhinosinusitis (OR 3.12) statistically increased the risk for extensive BE (Table 4). However, when studying the aetiology for extensive BE in non-smokers, idiopathic was the most common finding (18 patients, 42% of the non-smokers with extensive BE), followed by asthma (16 patients, 37%) (Table 5). Of the total of 65 patients with asthma, 51 (78.5%) had been tested for ABPA and two had suffered from ABPA. In 65 patients with asthma, 13 (20%) had increased specific IgE level for Aspergillus fumigatus, total-IgE levels were 750–1000 kU/l in one, 300–500 kU/l in two, and three patients had raised IgG level against *Aspergillus fumigatus*. The other patients with increased specific IgE level for *A. fumigatus* were considered to have asthma with fungal sensitization.

In the group of asthma as aetiology of BE, there was a mean of 18.5 years between the diagnosis of asthma and BE (Table 6). In three patients, asthma had been diagnosed in childhood. Further, either diagnostic bronchodilator response in spirometry or in PEF recording in medical records was found in 48% of the patients.

In the total BE cohort, 22 (23%) had experienced Pseudomonas aeruginosa colonisation of sputum now or earlier. Other reported sputum colonisations were Achromobacter (n = 1), Haemophilus (4), Serratia (3), M avium (2), M intracellulare (1), Staph aureus (2), Klebsiella (1), Moraxella (1), Morganella (1), Stenotrophomans (1), and Enterobacter (1). Moreover, when considering infections and immunodeficiencies in the total BE cohort, we found one patient with CVI (common variable immunodeficiency disease), nine patients with IgG subclass deficiency, one with selective IgA deficiency, one with T-cell deficiency with combined deficiencies, and one with secondary immunodeficiency.

When studying further the association of BE to connective tissue diseases (in addition to rheumatic disease) and inflammatory bowel disease, we found two patients with polymyalgia rheumatica, one with relapsing polychondritis, three with Sjögren syndrome, and two with ulcerative colitis.

4. Discussion

In the Finnish BE study population, with a mean age of 69 years, 26% had aetiology of asthma for BE. In these patients, asthma was diagnosed before BE. Asthma was found as a comorbidity and

Table 2
Aetiological diagnosis and comparison with prospective studies.

Underlying aetiology	Finland 2018 (n = 95)			UK 2006 (n = 165)			Greece 2016 (n = 277)			Spain 2017 (n = 2047)		
	%	Cl %	n	%	Cl %	*p* value	%	Cl %	*p* value	%	Cl %	*p* value
Idiopathic	41	29–55	39	26	17–35	< 0.01	34	27–41	0.16	24.2	22–27	< 0.01
Asthma	26	12.5–35	25	NA			2.5	0.1–4.9	< 0.01	5.4	4.1–6.7	< 0.01
Postinfectious	11	2–18	10	32	23–42	< 0.01	25.2	18–32	< 0.01	30	27–33	< 0.01
CTD	6	−0.28–12	6	2	−0.08–4.8	0.61	3.6	0.7–6.5	0.32	1.4	0.7–2	< 0.01
IgG deficiency	3	−1.5–7.5	3	7	1.9–12	0.18	3.6	0.7–6.5	0.32	9.4	7.7–11	0.03
Non-TB	3	−1.5–7.5	3	2[a]	−0.08–4.8	0.61	NA			NA		
Aspiration	2	−1.7–0.6	2	1	−1–3	0.5	NA			0.9	0.4–1.4	0.28
ABPA	2	−1.7–0.6	2	8	0.02–0.13	0.05	NA			0.9	0.00–0.01	0.28
Williams-Campbell sdr.	1	−1.6–3.6	1	NA			NA			NA		
PCD	1	−1.6–3.6	1	17	0.09–0.25	< 0.01	1.8	−2.6–3.9	0.59	2.9	0.02–0.04	0.27
COPD	1	−1.6–3.6	1	NA			6.5	2.7–10	0.04	7.8	6.3–9.3	0.01
TB	1	−1.6–3.6	1	NA			22.3			18.6		
Alpha-1-antitrysin def.	1	−1.6–3.6	1	NA			NA			0.5	0.1–0.9	0.51
IBD	NA			3			NA			0.2		
Young's sdr.	NA			3			NA			0.2		
Pan Bronkiolitis	NA			2			NA			0.1		
Yellow nail sdr.	NA			2			NA			0.2		
Cystic fibrosis	NA			1			NA			12.5		

Underlying aetiology	Portugal 2014 (n = 202)			France 2016 (n = 311)			Belgium 2012 (n = 539)			EU 2015 (n = 1258)		
	%	Cl %	*p* value	%	Cl %	*p* value	%	Cl %	*p* value	%	Cl %	*p* value
Idiopathic	57.4	48–66	0.01	11	6.4–16	< 0.01	26	21–31	< 0.01	40	36–44	0.7
Asthma	NA			4	1.1–6.9	< 0.01	NA			3.3	2–4.6	< 0.01
Postinfectious	NA			50	42–57		15	11–19	< 0.01	20	17–22	0.02
CTD	1.4	−0.7–3.5	0.03	3	0.5–5.5	0.18	7	4–10	0.72	10	7.8–12	0.2
IgG deficiency	3.5	1.7–6.8	0.82	6	2.5–9.5	0.25	5	2.6–7.4	0.4	5.8	4–7.5	0.25
Non-TB	NA			NA			0.9	−0.2–2.0	0.09	NA		
Aspiration	1	−0.8–2.8	0.48	NA			0.6	−0.03–1.5	0.16	0.6	0.01–0.012	0.11
ABPA	0.5	0.00–0.02	0.22	NA			5	0.03–0.07	0.19	3.3	0.02–0.05	0.49
Williams-Campbell sdr.	NA			NA			0.2	−0.3–0.7	0.2	NA		
PCD	0.5	0.00–0.02	0.62	NA			5	0.03–0.07	0.08	1.7	0.01–0.03	0.61
COPD	NA			13	8–18	< 0.01	12	8.4–16	< 0.01	15	12–18	< 0.01
TB	NA			NA			6.7			NA		
Alpha-1-antitrysin def.	NA			NA			0.4	−0.3–1	0.44	0.6	−0.01–1	0.63
IBD	NA			NA			1.7			1.9		
Young's sdr.	NA			NA			NA			NA		
Pan Bronkiolitis	NA			NA			NA			0.1		
Yellow nail sdr.	NA			NA			NA			NA		
Cystic fibrosis	1.4			NA			NA			NA		

CTD = Connective tissue disease; TB = Tuberculosis; COPD = Chronic Obstructive Pulmonary Disease; PCD = Primary Cilia Dyskinesia; ABPA = Allergic Bronchopulmonary Aspergillosis, IBD = Inflammatory Bowel Disease.
CI = Confidence Interval; P -value (Significance level 0.01). [a]TB and Non-TB.

Table 3
Characteristics of the BE patients with asthma as aetiology for BE.

	Asthma and BE (n = 25)		Other and BE (n = 70)		*p* value
Age, years, median (IQR)	74	(66–79)	71	(62.8–76)	0.1[a]
BMI, kg/m^2 median (IQR)	28.5	(25.1–30.9)	24.2	(21.5–28.6)	< 0.01[a]
Gender, female, n (%)	20	(80)	55	(78.57)	0.88
Current smoker, n (%)	0	(0)	3	(4.29)	0.29
Ex-smoker, n (%)	8	(32)	21	(30)	0.85
HRCT ≥ 4 lobes affected, n (%)	22	(88)	43	(61.4)	0.03
Cystic bronchiectasis, n (%)	1	(4)	8	(11.43)	0.28
Gastroesophageal reflux disease, n (%)	9	(36)	16	(22.86)	0.20
Exacerbations without hospitalization, mean (IRQ)	1.92	(1.66)	1.64	(1.55)	0.46[a]
Exacerbations with hospitalizations, mean (IQR)	1.2	(1.91)	0.53	(1.1)	0.06[a]
FEV1, % predicted, mean (± SD)	90.3	(19.9)	86.3	(25.6)	0.50
FVC, % predicted, mean (± SD)	99.1	(18.9)	98.4	(21.7)	0.88

HRCT = High resolution computed tomography; FEV1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity.
z-test was used to compare proportions. Independent samples *t*-test and Mann-Whitney U -test ([a]) were used to compare means and mean ranks respectively.

secondary to BE in 45% of the patients. The common other co-morbidities were cardiovascular diseases (30%) and gastroesophageal reflux disease (26%). Radiological cystic BE was found in only 9.4% of the patients. Compared to other BE cohorts, asthma was found approximately 5–10 times more often as aetiology in Finland. Likewise, post-infectious BE was 1.5–5 times more common in other BE cohorts compared to Finland. Risk factors for extensive BE were asthma, either as comorbidity or aetiology, and rhinosinusitis.

Asthma was considered significantly more often as aetiology for BE in Finland (26%) than in Greece (2.5%), France (4.0%), or Spain (5.4%) (Table 2) [4,9,10]. Exceptionally, in Portugal and in Belgium there were no asthma-driven cases of BE, although the prevalence of asthma is almost the same in Europe [12,13]. The worldwide comprehensive meta-analysis (N = 8608) has only 1.4% asthma driven BE [14]. In the US BE Registry, asthma was found as a comorbidity in 29% of 1826 BE patients [1]. These divergencies might be explained by differences in

Table 5
Aetiology for extensive BE in non-smokers.

Aetiology	n	%
Aspiration	1	2.3
Asthma	16	37.2
Connective tissue disease	2	4.7
Idiopathic	18	41.9
IgG subclass deficiency	1	2.3
PCD	1	2.3
Postinfectious	2	4.7
Rheumatoid arthritis	1	2.3
Tuberculosis	1	2.3
Total	43	100.0

PCD = Primary Cilia Dyskinesia.

Table 4
Risk factors for multilobe (HRCT ≥ 4 lobes affected) BE.

				Logistic Regression (age and gender adj.)		
	Crude-OR	95% CI for EXP	*p* value	OR	95% CI for EXP	*p* value
Age	1.02	0.99–1.06	0.17			
Gender	0.82	0.29–2.33	0.71	1.02	0.99–1.06	0.17
BMI	1.02	0.94–1.11	0.69			
FEV1 (%)	1.00	0.99–1.02	0.49			
FVC (%)	1.01	0.99–1.04	0.28			
Ever-smokers	5.25	0.42–66.22	0.20	5.21	0.41–66.06	0.20
Non-smokers	4.30	0.37–50.25	0.25	4.29	0.36–50.68	0.36
Chronic sputum production	2.26	0.74 - 6-61	0.14	2.62	0.86–8.04	0.09
Pseudomonas	3.72	1.01–13.74	0.49			
Diabetes, type2	1.02	0.94–1.11	0.69			
Asthma	2.68	1.08–6.68	0.03	2.65	1.06–6.67	0.04
Asthma as an aetiology	4.60	1.26–16.87	0.02	4.25	1.15–15.75	0.03
Cardiovascular disease	0.71	0.29–1.78	0.47			
Psychiatric disease	4.66	0.56–38.6	0.15	6.07	0.7–52.9	0.10
Nasal Polyps	2.04	0.53–7.84	0.30	3.71	0.85–16.11	0.08
Rhinosinusitis	2.67	0.96–7.42	0.06	3.12	1.1–9.05	0.04
Connective tissue disease	0.91	0.25–3.30	0.89			
Inflammatory bowel disease	0.45	0.03–7.50	0.58			
Immunodeficiency	2.25	0.46–11.12	0.32			
Gastroesophageal reflux disease	0.76	0.29–2.00	0.58			
Aspiration	2.42	0.27–21.64	0.43	2.18	0.24–19.76	0.49

BMI = Body Mass Index; FEV1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity.

Table 6
Detailed information on asthma history of those BE patients who were considered to have asthma as aetiology for BE.

	N = 25	%
Diagnostic bronchodilator response in spirometry	8	33
Diagnostic bronchodilator response or diurnal variation in PEF	7	28
Diagnostic spirometry or PEF recording[a]	12	48
Serum total IgE		
Serum total IgE elevated	5	20
Serum total IgE normal	9	36
IgE against Aspergillus fumigatus elevated	5	20
Asthma diagnosed in childhood	3	12
Asthma diagnosed years before BE diagnosis, not specified	8	32
Years between asthma and BE diagnosis, mean (SD, min-max)	18.5 (16.1; 1–60)	

[a] For others information of pulmonary function tests performed at the time of asthma diagnosis was not available because of the long time-interval between asthma and BE diagnoses.

diagnosis of asthma and BE. It seems possible that there are regional differences in how often the patients with mild asthma symptoms or seasonal asthma symptoms are diagnosed with asthma. Further, it is well known that prevalence of asthma varies in different populations, but it has also been shown to differ in the same population in respect to time [15–17].

We considered asthma as an aetiology factor to BE if asthma was diagnosed earlier than BE. However, BE might also be associated to recurrent respiratory infections in an asthma patient. In severe asthma, BE increases hospitalization rate with OR 2.09 compared to asthma without BE [18]. The British Thoracic Society recommends asthma to be considered as a cause of BE if no other specific cause is found [19]. Similarly, if BE in association with asthma is reported to carry poorer survival and a greater exacerbation rate than asthma alone then also asthma in association with BE has been reported to increase significantly the BE exacerbation risk (OR 2.6, 95% CI 1.15–5.88) [20]. This is in accordance with our finding of asthma increasing the risk for extensive BE and exacerbations with hospitalizations (1.2 in BE and asthma, and 0.53 in BE with other background aetiologies) (Table 4).

Likewise, when COPD was defined aetiology of BE in 1.0% in the Finnish study; there were 6.5% in Greece, 7.8% Spanish, 12.0% Belgian, 13.0% French, and 15.0% in EU and none in the British and Portuguese study [3,4,9–13]. COPD was found in 8.0% of BE patients and in 1% of BE patients COPD were estimated as aetiology. In those with COPD only as comorbidity, COPD was mild and there were other aetiology factors for BE.

Extensive BE is characterized as those with four or more lobes affected. In our study, extensive HRCT findings had 68% of the BE patients whereas in the USA registry data 48% had extensive radiographic findings [1]. Further, the right upper lobe was the most involved (57%) and left upper lobe the least involved (44%), whereas in our study the right basal lobe was the most often affected (88%) and the left upper lobe was the least often affected (31%).

Postinfectious aetiology of BE in Finland (11%) was more rare than elsewhere: Belgium (15%), EU (20%), Greece (25%), Spain (30%), UK (32%) and France (50%) [3,4,9–12]. These comparisons introduce a possibility that patients with recurrent airway infections might have had undiagnosed and untreated asthma. In Turkey, primary ciliary dysfunction, immunodeficiency, and history of tuberculosis were the most common background causes for BE in patients under 19 years-of-age, highlighting different regional genetical and environmental infection factors [21,22]. The radiographic findings support the data in the medical records regarding infections and tuberculosis being rather rare in our study population since 3.2% of the study individuals had only one lobe, and 15.8% two lobes, affected. In addition to 11% of post-infectious BE, 5% of our study population had experienced tuberculosis.

GERD (gastroesophageal reflux disease) has been associated with BE, asthma, and chronic cough. In the US BE Registry, GERD was found as comorbidity in 47% of 1826 BE patients [1]. In our study, 26% had GERD and daily proton pump inhibitor (PPI) use. Diagnosis of GERD was based on the information in medical records. The BE study protocol did not include esophageal pH-monitoring. Proton pump inhibitors (PPI) reduce reflux symptoms and acidity but may not inhibit micro aspiration. Regardless of reflux symptom relief, PPIs have not been shown effective for cough or asthma symptoms [23,24]. Fundoplication as a therapeutic option for GERD has been shown to prevent also aspiration.

Not only GERD, but also hiatal hernia is associated to BE and especially to its severity [25]. The presence of hiatal hernia has been reported to associate with cystic BE, increased number of lobes involved, increased extent of BE, and reduced lung function. In our cohort, 6% had been diagnosed aspiration and 2% of those was estimated as aetiology for BE. The incidence was at the same level compared with other European studies [4,11–13].

The population was recruited from three Helsinki University Hospital Pulmonary Clinic at three hospitals and one of the study sites is the Allergy Department. This may affect the large proportion of asthma both as aetiology and as comorbidity for BE. It is also possible that elsewhere mild intermittent or even mild persistent asthma is considered as recurrent respiratory infections if diagnostic procedures are different. Because of the reimbursement system of asthma medication, Finnish asthma patients are diagnosed carefully according to symptoms and lung function parameters. It is most likely that diagnostic procedure is more thorough in Finland when compared to countries where asthma is diagnosed according to self-reported symptoms only. In those patients, who were considered to have asthma as aetiology of BE, detailed information on lung function parameters was not available for all the patients because of long time interval between asthma and BE diagnoses, or because asthma had been diagnosed elsewhere. The time interval between asthma and BE diagnoses was quite long, a mean of 18.5 years.

All these results remind us of the importance of a systematic approach also in association to BE. Infectious disease history, screening of immunodeficiency, rheumatoid arthritis and other connective tissue diseases, aspiration, obstructive lung diseases (both asthma and COPD) and ABPA should be evaluated.

5. Conclusions

Asthma is common as aetiology and comorbidity in BE and should be considered in diagnostics and treatment. BE in association with asthma has been reported to carry a poorer survival and a greater exacerbation rate than asthma alone. Both obstructive lung diseases were found in 77% of BE patients. Other co-morbidities were cardiovascular disease (30%) and gastroesophageal reflux (26%). Asthma either as aetiology or comorbidity, or rhinosinusitis, increased the risk for extensive BE.

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